

What is claimed is:

- Fig 23 >
- 1 1. A method for identifying an OP-1 receptor-binding analog, said  
2 analog being characterized as having substantially the same  
3 binding affinity for a cell surface receptor as OP-1, the method  
4 comprising the steps of:
- 5 (a) providing a sample containing a protein selected from the group  
6 consisting of:
- 7 (i) a polypeptide chain comprising an amino acid sequence  
8 defined by residues 16-123 of Seq. ID No. 3 (ALK-2), or an  
9 OP1-binding analog thereof;
- 10 (ii) a polypeptide chain comprising an amino acid sequence  
11 defined by residues 24-152 of Seq. ID No. 5 (ALK-3),, or an  
12 OP1-binding analog thereof;
- 13 (iii) a polypeptide chain comprising an amino acid sequence  
14 defined by residues 23-122 of Seq. ID No. 7 (ALK-6),, or an  
15 OP1 binding analog thereof;
- 16 (iv) a polypeptide chain having binding affinity for OP-1 and  
17 sharing at least 40% amino acid identity with residues 23-  
18 122 of Seq. ID No. 7 (ALK-6),;
- 19 (v) a polypeptide chain having binding affinity for OP-1 and  
20 encoded by a nucleic acid obtainable by amplification with  
21 one or more primer sequences defined by Seq. ID Nos. 12-15;  
22 or
- 23 (vi) a polypeptide chain having binding affinity for OP-1 and  
24 encoded by a nucleic acid that hybridizes under stringent  
25 conditions with a nucleic acid comprising the sequence  
26 defined by nucleotides 256-552 of Seq. ID No. 7 (ALK-6),;
- 27 (b) contacting said sample with a candidate OP1 receptor- binding  
28 analog; and
- 29 (c) detecting specific binding between said candidate OP1 receptor-  
30 binding analog and said protein.
- 1 2. A method for identifying an OP-1 receptor-binding analog, said  
2 analog being characterized as having substantially the same  
3 binding affinity for a cell surface receptor as OP1, the method  
4 comprising the steps of:

FOOTNOTES

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- 5 (a) providing a cell that expresses a surface receptor protein having  
6 binding specificity for OP-1 selected from the group consisting  
7 of:  
8 (i) a polypeptide chain comprising an amino acid sequence  
9 defined by residues 16-123 of Seq. ID No. 3 (ALK-2), or an  
10 OP1-binding analog thereof;  
11 (ii) a polypeptide chain comprising an amino acid sequence  
12 defined by residues 24-152 of Seq. ID No. 5 (ALK-3),, or an  
13 OP1-binding analog thereof;  
14 (iii) a polypeptide chain comprising an amino acid sequence  
15 defined by residues 23-122 of Seq. ID No. 7 (ALK-6),, or an  
16 OP1 binding analog thereof;  
17 (iv) a polypeptide chain having binding affinity for OP-1 and  
18 sharing at least 40% amino acid identity with residues 23-  
19 122 of Seq. ID No. 7 (ALK-6),;  
20 (v) a polypeptide chain having binding affinity for OP-1 and  
21 encoded by a nucleic acid obtainable by amplification with  
22 one or more primer sequences defined by Seq. ID Nos. 12-15;  
23 or  
24 (vi) a polypeptide chain having binding affinity for OP-1 and  
25 encoded by a nucleic acid that hybridizes under stringent  
26 conditions with a nucleic acid comprising the sequence  
27 defined by nucleotides 256-552 of Seq. ID No. 7 (ALK-6),;  
28 (b) contacting said cell with a candidate OP1 receptor-binding  
29 analog; and  
30 (c) detecting induction of an OP-1-mediated cellular response.

1 3. The method of claim 2 wherein said OP-1 mediated cellular response  
2 detected in step (c) is induction of a kinase activity, inhibition of  
3 epithelial cell growth, or induction of a cell differentiation  
4 marker.

1 4. The method of claim 2 or 3 wherein said cell comprises a transfected  
2 nucleic acid comprising a reporter gene in operative association with a  
3 control element derived from an OP-1 inducible protein.

1 5. The method of any of claims 1-4 wherein said sample further comprises  
2 part or all of a Type II serine/threonine kinase receptor protein  
3 having binding affinity for OP-1, activin or BMP-4.

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- 1 6. A method for producing an OP-1 receptor binding analog, the method  
2 comprising the steps of:
- 3 (a) obtaining, by the method of any of claims 1-5, a candidate OP-1  
4 binding analog, and
- 5 (b) producing either said candidate analog or a second OP-1 binding  
6 analog derived from said candidate and having substantially the  
7 same OP-1 receptor-binding domain as said candidate.
- 1 7. The method of producing an OP-1 receptor-binding analog of claim 6  
2 wherein said analog produced in step (b) is by recombinant DNA  
3 techniques, or by nonbiological peptide synthesis.
- 1 8. A kit for identifying OP-1 or a candidate OP-1 receptor binding analog  
2 in a sample, the kit comprising:
- 3 (a) a receptacle adapted to receive a sample and containing a protein  
4 selected from the group consisting of:
- 5 (i) a polypeptide chain comprising an amino acid sequence  
6 defined by residues 16-123 of Seq. ID No. 3 (ALK-2), or an  
7 OP1-binding analog thereof;
- 8 (ii) a polypeptide chain comprising an amino acid sequence  
9 defined by residues 24-152 of Seq. ID No. 5 (ALK-3),, or an  
10 OP1-binding analog thereof;
- 11 (iii) a polypeptide chain comprising an amino acid sequence  
12 defined by residues 23-122 of Seq. ID No. 7 (ALK-6),, or an  
13 OP1 binding analog thereof;
- 14 (iv) a polypeptide chain having binding affinity for OP-1 and  
15 sharing at least 40% amino acid identity with residues 23-  
16 122 of Seq. ID No. 7 (ALK-6),;
- 17 (v) a polypeptide chain having binding affinity for OP-1 and  
18 encoded by a nucleic acid obtainable by amplification with  
19 one or more primer sequences defined by Seq. ID Nos. 12-15;  
20 or
- 21 (vi) a polypeptide chain having binding affinity for OP-1 and  
22 encoded by a nucleic acid that hybridizes under stringent  
23 conditions with a nucleic acid comprising the sequence  
24 defined by nucleotides 256-552 of Seq. ID No. 7 (ALK-6),;  
25 and
- 26 (b) means for detecting interaction of OP-1 or a candidate OP-1  
27 receptor-binding analog with said protein of part (a), said OP-1

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28 or candidate analog comprising part of said sample provided to  
29 said receptacle.

- 1 9. The kit of claim 8 wherein said means in part (b) comprises either  
2 (i) means for detecting specific binding interaction of OP-1  
3 or said candidate analog with said protein; or  
4 (ii) means for detecting induction of an OP-1 mediated cellular  
5 response.

10. The kit of claim 8 or 9 further comprising a serine/threonine Type II  
2 receptor having binding specificity for OP-1, activin or BMP-4.

1 11. An OP-1 receptor-binding analog produced by the method of any of claims  
2 1-7 or use of the kit of claims 8-10.

1 12. The analog produced by the method of any of claims 1-8, said analog  
2 (i) comprising an amino acid sequence sharing greater than 60%  
3 identity with the C-terminal 96 amino acids of the sequence  
4 represented by Seq. ID No. 9 (OP-1, residues 335-431), and  
5 (ii) being substantially incapable of inducing an OP-1 mediated  
6 cellular response.

1 13. The analog of claim 11 or 12 further having binding affinity for a  
2 Type II serine/threonine kinase cell surface receptor.

1 14. The analog of claim 13 wherein said Type II receptor also has binding  
2 affinity for activin or BMP-4.

1 15. An isolated ligand-receptor complex comprising two molecules  
2 interacting as specific binding partners, the first said molecule  
3 defining said ligand and comprising at least the C-terminal 96 amino  
4 acids of OP1 (residues 335-431 of Seq ID No. 9) or a receptor-binding  
5 analog thereof, and the second said molecule defining said receptor and  
6 being selected from the group consisting of:

7 (i) a polypeptide chain comprising an amino acid sequence  
8 defined by residues 16-123 of Seq. ID No. 3 (ALK-2), or an  
9 OP1-binding analog thereof;

10 (ii) a polypeptide chain comprising an amino acid sequence  
11 defined by residues 24-152 of Seq. ID No. 5 (ALK-3), or an  
12 OP1-binding analog thereof;

13 (iii) a polypeptide chain comprising an amino acid sequence  
14 defined by residues 23-122 of Seq. ID No. 7 (ALK-6), or an  
15 OP1 binding analog thereof;

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- 16 (iv) a polypeptide chain having binding affinity for OP-1 and  
17 sharing at least 40% amino acid identity with residues 23-  
18 122 of Seq. ID No. 7 (ALK-6),;
- 19 (v) a polypeptide chain having binding affinity for OP-1 and  
20 encoded by a nucleic acid obtainable by amplification with  
21 one or more primer sequences defined by Seq. ID Nos. 12-15;  
22 or
- 23 (vi) a polypeptide chain having binding affinity for OP-1 and  
24 encoded by a nucleic acid that hybridizes under stringent  
25 conditions with a nucleic acid comprising the sequence  
26 defined by nucleotides 256-552 of Seq. ID No. 7 (ALK-6),.
- 1 16. The complex of claim 15 further comprising part or all of a Type II  
2 serine/threonine kinase receptor .
- 1 17. The complex of claim 16 wherein said Type II receptor also has binding  
2 affinity for activin or BMP-4.
- 1 18. The complex of any of claims 15-17 wherein said first molecule defining  
2 said ligand is an OP-1 receptor-binding analog comprises part or all  
3 of the proteins selected from the group consisting of 60A, BMP-5, BMP-  
4 6, Vgr-1, OP2, OP3 and receptor-binding amino acid sequence variants or  
5 xenogenic homologs thereof.
- 1 19. An isolated binding partner having specific binding affinity for an  
2 epitope on a ligand-receptor complex, said complex being characterized  
3 as comprising an OP-1 protein or an analog thereof in specific binding  
4 interaction with the ligand binding domain of a cell surface receptor  
5 defined by Seq. ID No. 3 (ALK-2), 5, or 7, or an OP1-binding analog  
6 thereof; said binding partner having substantially no binding affinity  
7 for the uncomplexed form of said OP-1 protein or OP-1 protein analog.
- 1 20. The isolated binding partner of claim 19 wherein said binding partner  
2 is further characterized as having substantially no binding affinity  
3 for the uncomplexed form of said cell surface receptor protein or said  
4 analog thereof.
- 1 21. The binding partner of claim 19 wherein said binding partner is a  
2 monoclonal or polyclonal antibody.
- 1 22. Use of the OP-1 receptor-binding analog of any claims 11-14 in a method  
2 for
- 3 (i) antagonizing OP-1 binding to a cell surface receptor; or  
4 (ii) antagonizing induction of an OP-1 mediated cellular  
5 response.

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23. The use according to claim 22 wherein said OP-1 receptor-binding analog comprises an antibody having binding specificity for
- (i) the ligand binding domain of a cell surface receptor defined by Seq. ID Nos. 3, 5, or 7 or an OP-1 binding analog thereof; or
  - (ii) the receptor binding domain of OP-1, represented by Seq. ID No. 9, or a receptor-binding analog thereof.
24. Use of a protein selected from the group consisting of:
- (i) a polypeptide chain comprising an amino acid sequence defined by residues 16-123 of Seq. ID No. 3 (ALK-2), or an OP1-binding analog thereof;
  - (ii) a polypeptide chain comprising an amino acid sequence defined by residues 24-152 of Seq. ID No. 5 (ALK-3), or an OP1-binding analog thereof;
  - (iii) a polypeptide chain comprising an amino acid sequence defined by residues 23-122 of Seq. ID No. 7 (ALK-6), or an OP1 binding analog thereof;
  - (iv) a polypeptide chain having binding affinity for OP-1 and sharing at least 40% amino acid identity with residues 23-122 of Seq. ID No. 7 (ALK-6),;
  - (v) a polypeptide chain having binding affinity for OP-1 and encoded by a nucleic acid obtainable by amplification with one or more primer sequences defined by Seq. ID Nos. 12-15; or
  - (vi) a polypeptide chain having binding affinity for OP-1 and encoded by a nucleic acid that hybridizes under stringent conditions with a nucleic acid comprising the sequence defined by nucleotides 256-552 of Seq. ID No. 7 (ALK-6),;
- in a method for antagonizing
- (i) OP-1 binding to a cell surface receptor; or
  - (ii) induction of an OP-1 mediated cellular response.
25. A method for antagonizing activin binding to a cell surface receptor, the method comprising the step of:
- providing a cell expressing a said receptor with a protein having binding specificity for the amino acid sequence defined by residues 16-123 of Seq ID No. 3 or an OP-1 binding sequence variant thereof, said protein sharing at least 60% amino acid

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